ATF6 is essential for human cone photoreceptor development.

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Public Summary:
Achromatopsia is a retinal degeneration where people have severely impaired daytime vision and color bindness. There are no treatments for the disease. Previously, our research group identified ATF6 gene mutations in families with achromatopsia. In our current paper, we generated stem cells from these achromatopsia families carrying ATF6 mutations. We differentiated the patient stem cells into retinal organoids to study how ATF6 affected the retinal neurons responsible for diurnal and color vision. We discovered that retinal organoids from the achromatopsia patients with ATF6 mutations failed to generate normal cone photoreceptors. Cone photoreceptors are the retinal neuron cell type required for diurnal and color vision. We used advanced retinal imaging in our ATF6 donor patients and confirmed that cone photoreceptor structures were also defective in these patients. These studies reveal that ATF6 is essential for human cone formation, and ATF6 mutations cause achromatopsia because cones do not form in patient retinas. Next, we tested if small molecule proteostasis compounds could help cones form in our ATF6 patients' retinal organoids. We identified a small molecule proteostasis compound, AA147, could robustly restore the biochemical function of Class 1 ATF6 patient variants in vitro. We found that patient retinal organoids treated with this compound showed increased development of cone photoreceptors by transcriptomic and morphologic parameters. Our findings provide proof-of-principle that small molecule proteostasis strategy can help diseased cones in retinal organoids and should be further studied as a potential treatment in achromatopsia patients.

Scientific Abstract:
Endoplasmic reticulum (ER) stress and Unfolded Protein Response (UPR) signaling promote the pathology of many human diseases. Loss-of-function variants of the UPR regulator Activating Transcription Factor 6 (ATF6) cause severe congenital vision loss diseases such as achromatopsia by unclear pathomechanisms. To investigate this, we generated retinal organoids from achromatopsia patient induced pluripotent stem cells carrying ATF6 disease variants and from gene-edited ATF6 null hESCs. We found that achromatopsia patient and ATF6 null retinal organoids failed to form cone structures concomitant with loss of cone phototransduction gene expression, while rod photoreceptors developed normally. Adaptive optics retinal imaging of achromatopsia patients carrying ATF6 variants also showed absence of cone inner/outer segment structures but preserved rod structures, mirroring the defect in cone formation observed in our retinal organoids. These results establish that ATF6 is essential for human cone development. Interestingly, we find that a selective small molecule ATF6 signaling agonist restores the transcriptional activity of some ATF6 disease-causing variants and stimulates cone growth and gene expression in patient retinal organoids carrying these variants. These findings support that pharmacologic targeting of the ATF6 pathway can promote human cone development and should be further explored for blinding retinal diseases.